

REMARKS

Status of the Claims

Claim 26 has been amended. Claims 32 and 34 have been canceled without prejudice or disclaimer. Claims 26-31, 33, and 35-39 are in the case.

Information Disclosure Statement

The Examiner did not initial the references listed on page 5 of the previously submitted PTO form 1449. This appears to be an oversight. Applicant requests the Examiner to indicate that those references, MMM-BBBB were considered.

Rejections Under 35 USC §112, 1st ¶

The Action rejects claims 26-39 as allegedly failing to comply with the enablement requirement, relying primarily on art that indicates issues in delivering therapeutic agents to solid tumors.

Applicant asserts that, to the contrary, the Specification is fully enabling for the claimed subject matter. None of the cited art, either alone or in combination refutes the description in the Specification that inhibition of caveolin with antibody therapy would be beneficial in the treatment of neoplastic disease of the prostate, and more particularly that such treatment would inhibit metastasis as in claim 26, or restore androgen dependence as in claim 35.

The Specification states in [0017] that caveolin expression increases in metastatic human prostate cells as compared to primary tumors and that agents to block the activity of caveolin in metastatic cells or cells predisposed to metastasis would be useful in treatment of human prostate tumors. The Specification further describes treating prostate cancer and metastatic prostate disorders by administering an anti-caveolin antibody, at least at paragraphs [0019] [0077] [0079] [0080] [0087] [0090] and [0095], all of which teach one of skill in the art that suppression of caveolin activity is useful in the treatment of metastatic prostate cancer and prostate neoplasia

with potential to progress to become metastatic. Although the *in vivo* data was obtained by genetic suppression of caveolin, either by antisense or knockout constructs, one of skill in the art clearly understands that the suppression of caveolin activity can also be achieved by the use of antibody therapy as described. The use of anti-caveolin antibodies in inhibition of metastasis in prostate disease is thus fully enabled.

The method of claim 35, inhibiting caveolin activity concurrently with androgen depletion therapy, is also fully enabled by the Specification.

It is an important aspect of the disclosure that inhibiting expression or activity of caveolin restores androgen sensitivity to prostate cancer. It is well known that prostate cancer is androgen dependent, or in other words, prostate cancer will not grow in the absence of androgen, and a primary treatment for prostate cancer includes androgen deprivation. Certain tumors, however, become androgen insensitive and no longer require androgen to grow. When this occurs, the tumor no longer responds to one of the most effective available treatment options. Restoring androgen sensitivity by concurrently suppressing caveolin and androgen is an important and novel contribution to the art. This effect and combination therapy are described in the Specification at least at paragraphs [0021] [0079] [0081] [0085] and [0117]. The treatment of prostate cancer by suppressing caveolin with an anticaveolin antibody in conjunction with reducing androgen levels, therefore, is fully enabled by the Specification.

Furthermore, it is known that anti-caveolin antibodies are available and a physician of skill in this art would require no undue experimentation to prepare and administer antibody therapy as described. It is further understood that treatment regimens and dosages for antibody therapies are known in the art and that specific treatments are determined in human clinical trials as approved by the FDA. Such human clinical trial data is not required for purposes of patentability.

The references relied on by the Action do not refute the enablement of Applicant's asserted utility.

Jain describes some obstacles to systemic delivery of cytotoxic chemicals to solid tumors at concentrations sufficient to eliminate the malignancies from the body. Such a discussion is not relevant to the claimed inventions, which are not necessarily directed to total elimination of a primary tumor. Jain, for example, does not discuss the possibility of treating a prostatic disease by inhibiting the function of a protein such as caveolin, or inhibiting progression of the disease to a metastatic state, but focuses the discussion on achieving lethal concentrations of a cytotoxic agent throughout a solid tumor.

The Action also cites Dillman, a review article about treatment with monoclonal antibodies that was written in 1989, when monoclonal antibody therapy was a relatively new technology. Even the Dillman abstract states that monoclonal antibodies are a promising therapy but that their general use will be delayed for several years. It has now been sixteen years since Dillman made that statement. One of skill in the art would not look to such a dated review article when evaluating a therapeutic approach and would find nothing in the Dillman article that has any relevance to the present claims.

The Action also points to alleged major obstacles to antibody therapy in the Weiner article. The abstract of Weiner states, however, that monoclonal based therapeutics have shown efficacy in clinical trials, and further states that these exciting results justify the enthusiasm for continued efforts to refine the existing approaches. The Weiner reference thus argues for the enablement of the claims in spite of certain obstacles that Weiner states are not reason for discouragement. Turning to the more recent of the Dillman articles, the section entitled *Monoclonal Antibodies as Biologic Response Modifiers* beginning on page 1505 may have some relevance to the claimed invention, since inhibition of caveolin activity can be considered a

biologic response treatment, based on the data in the Specification in which the caveolin is genetically suppressed. This appears more relevant than the short discussion of treating prostate cancer with anti-PSA or anti-prostatic acid phosphatase. This review, written in 1994 indicates that such therapies including antibodies against receptors such as Her2-neu, transferring and epidermal growth factor were in very early stages of development thirteen years ago.

Applicants submit that none of the references discussed above are relevant to the enablement of the present claims, first because they are discussing a technology that has advanced significantly since their publication dates, and second because none of the references, even at those early dates, dispute the efficacy of antibody therapy as suggested by the Action.

The Action appears to mischaracterize Nelson, taking a single phrase out of context to state that Nelson teaches that reduced caveolin expression might be considered ineffective. When the statement is fully considered, as it would be by one of skill in the art, to learn what the author actually meant, the opposite conclusion is reached.

Although the progression of caveolin-depleted tumors is less than that of control, the tumors still progress. If a similar caveolin targeting strategy were successfully applied in humans using tumor growth as the endpoint, the therapy would be considered ineffective because the tumors would continue to grow, albeit more slowly. But prostate tumors are characterized by low rates of proliferation and apoptosis; **therefore, any therapy that prolongs survival deserves consideration.** This seemingly axiomatic concept has not enjoyed wide acceptance by those demanding evidence of cytotoxicity as the final measure of efficacy. Until a cure for prostate cancer is found, **new therapies producing disease stabilization should not be dismissed.** (Emphasis added) Nelson, pg 1011

The Lee article mentioned in the Action is now mute as the claims are limited to prostatic disease.

Nothing in any of the cited articles, therefore, would lead one of skill in the art to doubt the enablement of the present claims. Further support for the enablement is also provided in the

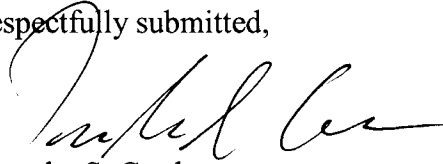
copies of Web pages attached hereto, indicating that Herceptin, a monoclonal antibody against the Her2-new receptor that is used as a biologic response modifier has been approved and is on the market. One of skill in the art, thus understands that such antibodies can be used in the treatment of cancers, and that would include prostate cancer as stated in the Application. The abstracts of two additional reports are also attached. In addition to Herceptin, monoclonal antibody blockage of the human Eag1 potassium channel function has shown positive results in clinical trials, and antitumor necrosis factor antibodies are both are reported to show favorable results *in vitro* and *in vivo*.

Applicants submit, therefore, that the difficulties discussed in the Action have been overcome and that the Specification is fully enabled. Any evidence presented by the Examiner has been rebutted.

Applicants respectfully submit that the claims are fully enabled and request withdrawal of all rejections under §112.


Applicant respectfully submits that the pending claims are in condition for allowance, and solicit an early indication to that effect. Should the Examiner have any questions, comments or suggestions that would more quickly progress the claims to allowance, the Examiner is invited to contact the undersigned representative at 512.542.8446.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Timothy S. Corder', written in a cursive style.

Timothy S. Corder
Reg. No. 38,414
Agent for Applicants

Vinson & Elkins L.L.P.
First City Tower
1001 Fannin
Suite 2300
Houston, Texas 77002-6760
512.542.8446
Date: September 20, 2007

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Herceptin is the first humanized antibody approved for the treatment of HER2-positive metastatic breast cancer. Herceptin is designed to target and block the function of HER2 protein overexpression.

Research has shown that HER2-positive breast cancer is a more aggressive disease with a greater likelihood of recurrence, a poorer prognosis, and a decreased chance of survival compared with HER2-negative breast cancer.

Status

Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. The U.S. Food and Drug Administration (FDA) approved Herceptin in September 1998. In November 2006, the FDA approved Herceptin as part of a treatment regimen containing doxorubicin, cyclophosphamide and paclitaxel, for the adjuvant treatment of patients with HER2-positive, node-positive breast cancer.

WARNINGS:**Cardiomyopathy**

Herceptin administration can result in left ventricular dysfunction and congestive heart failure (CHF). Left ventricular function should be evaluated in all patients prior to and during treatment with Herceptin.

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The incidence and severity of left ventricular cardiac dysfunction/CHF was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Discontinue Herceptin treatment in patients receiving adjuvant therapy for breast cancer and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function. (See **WARNINGS: Cardiomyopathy**, See **DOSAGE AND ADMINISTRATION: Dose Modifications in Full Prescribing Information**.)

Infusion Reactions**Pulmonary Toxicity**

Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Herceptin should be strongly considered for infusion reactions manifesting as anaphylaxis, angioedema, pneumonitis, or acute respiratory distress syndrome. (See **WARNINGS in Full Prescribing Information**.)

Herceptin[®] (Trastuzumab): Questions and Answers

Key Points

- Herceptin is a monoclonal antibody that attaches to proteins on some cancer cells and slows or stops the growth of the cells (see Question 1).
- Herceptin is used to treat HER-2 positive breast cancer (see Question 3).
- Some serious side effects, including heart muscle damage and allergic reactions, are associated with Herceptin (see Question 5).
- Herceptin is being studied in clinical trials (research studies) for the treatment of breast cancer and other types of cancer (see Question 6).

1. What is Herceptin? How does it work?

Herceptin (trastuzumab) is a monoclonal antibody. Antibodies are substances the body produces to help fight infection or other foreign particles. Monoclonal antibodies are made in the laboratory, and some are designed to attack specific cancer cells.

Herceptin targets cancer cells that “overexpress,” or make too much of, a protein called HER-2 or *erb* B2, which is found on the surface of some cancer cells. Herceptin attaches to the HER-2 positive cancer cells and slows or stops the growth of the cells. Herceptin is used only to treat breast cancers that are HER-2 positive. HER-2 positive cancers overexpress the HER-2 protein or have amplification (too many copies) of the HER-2 gene.

Approximately 20 to 30 percent of breast cancers overexpress HER-2. These tumors tend to grow faster and are generally more likely to recur (come back) than tumors that do not overproduce HER-2.



2. How are tumors tested for HER-2?

The amount of HER-2 protein in the tumor is measured in the laboratory using a test called immunohistochemical (IHC) analysis. The results of the test are measured on a scale from 0 (negative) to 3+ (strongly positive). Patients with tumors that are 3+ on the IHC test are most likely to benefit from Herceptin therapy; those with tumors that are 0 or 1+ are unlikely to benefit from this treatment. Patients with tumors that are 2+ often have an additional test, called fluorescence in situ hybridization (FISH), to determine whether the tumor is HER-2 positive. FISH measures the number of copies of a gene. Tumors with too many copies of the HER-2 gene as determined by the FISH test are considered positive.

3. How is Herceptin used in the treatment of cancer?

Herceptin is approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic breast cancer (breast cancer that has spread to other parts of the body) that is HER-2 positive. The FDA approved Herceptin after two clinical trials (research studies) with women whose metastatic breast cancers produced excess amounts of HER-2 demonstrated that Herceptin was safe and effective.

In 2005, the results of four clinical trials showed that Herceptin is also effective in the treatment of early-stage breast cancer that overexpresses HER-2. In all four studies, women who received Herceptin and chemotherapy lived longer and had significantly less chance of the breast cancer coming back than patients who received chemotherapy alone.

4. How is Herceptin given? What are some of the common side effects of Herceptin?

Herceptin is given by infusion (a method of putting fluids, including drugs, into the bloodstream). The first dose of Herceptin is usually given over a 90-minute period, and the nurse or doctor watches the patient for signs of side effects. If the patient tolerates this dose well, smaller maintenance doses can be given over a 30-minute period.

Side effects that most commonly occur during the first treatment with Herceptin include fever and/or chills. Other possible side effects include pain, weakness, nausea, vomiting, diarrhea, headaches, difficulty breathing, and rashes. These side effects generally become less severe after the first treatment with Herceptin.

Patients who receive Herceptin along with chemotherapy may experience side effects that are different from those of patients who take Herceptin by itself. For example, anemia (a condition in which the number of red blood cells is below normal) and infection, primarily mild upper respiratory infection, have been seen more often in patients given Herceptin with chemotherapy compared with those receiving Herceptin alone. Patients should discuss any concerns about the side effects of treatment with their doctor. The doctor may be able to make suggestions for managing side effects.

5. Can Herceptin cause any serious side effects?

Yes. Herceptin can cause heart muscle damage that can lead to heart failure. Heart failure is a serious condition in which the heart cannot pump enough blood throughout the body. Symptoms of heart failure include shortness of breath, difficulty breathing, and swelling of the feet or lower legs.

Herceptin can also affect the lungs, causing severe or life-threatening breathing problems that require immediate medical attention.

In addition, Herceptin can cause hypersensitivity (allergic) reactions that can be severe or life-threatening. Symptoms of a reaction include a drop in blood pressure, shortness of breath, rashes, and wheezing. Most patients who experience hypersensitivity reactions do so when the drug is being given or within 24 hours after treatment.

Because of these potentially life-threatening side effects, doctors evaluate patients carefully for any heart or lung problems before starting treatment. Doctors and nurses also monitor patients closely during treatment. Patients who develop any problems during or after treatment should call the doctor immediately or go to the nearest emergency care facility.

6. Is Herceptin still being studied in clinical trials?

Yes. Clinical trials are ongoing to test the safety and effectiveness of Herceptin for breast and other types of cancer. People interested in taking part in a clinical trial should talk with their doctor. Information about clinical trials is available from the National Cancer Institute's (NCI) Cancer Information Service (CIS) (see below) at 1-800-4-CANCER and in the NCI booklet *Taking Part in Clinical Trials: What Cancer Patients Need To Know*, which can be found at <http://www.cancer.gov/publications> on the Internet. This booklet describes how research studies are carried out and explains their possible benefits and risks. More information about clinical trials is available at <http://www.cancer.gov/clinicaltrials> on the NCI's Web site. The Web site offers detailed information about specific ongoing studies by linking to PDQ[®], the NCI's comprehensive cancer information database.

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Related Resources

Publications (available at <http://www.cancer.gov/publications>)

- National Cancer Institute Fact Sheet 7.2, *Biological Therapies for Cancer: Questions and Answers*
- National Cancer Institute Fact Sheet 7.49, *Targeted Cancer Therapies: Questions and Answers*
- *Taking Part in Clinical Trials: What Cancer Patients Need To Know*

National Cancer Institute (NCI) Resources

Cancer Information Service (toll-free)

Telephone: 1-800-4-CANCER (1-800-422-6237)

TTY: 1-800-332-8615

Online

NCI's Web site: <http://www.cancer.gov>

LiveHelp, NCI's live online assistance:

<https://cissecure.nci.nih.gov/livehelp/welcome.asp>

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1: Cancer Res. 2007 Aug 1;67(15):7343-9.

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Links

Monoclonal antibody blockade of the human Eag1 potassium channel function exerts antitumor activity.

Gómez-Varela D, Zwick-Wallasch E, Knötgen H, Sánchez A, Hettmann T, Ossipov D, Weseloh R, Contreras-Jurado C, Rothe M, Stühmer W, Pardo LA.

Max-Planck Institute of Experimental Medicine, Göttingen, Germany.

The potassium channel ether à go-go has been directly linked to cellular proliferation and transformation, although its physiologic role(s) are as of yet unknown. The specific blockade of human Eag1 (hEag1) may not only allow the dissection of the role of the channel in distinct physiologic processes, but because of the implication of hEag1 in tumor biology, it may also offer an opportunity for the treatment of cancer. However, members of the potassium channel superfamily are structurally very similar to one another, and it has been notoriously difficult to obtain specific blockers for any given channel. Here, we describe and validate the first rational design of a monoclonal antibody that selectively inhibits a potassium current in intact cells. Specifically blocking hEag1 function using this antibody inhibits tumor cell growth both in vitro and in vivo. Our data provide a proof of concept that enables the generation of functional antagonistic monoclonal antibodies against ion channels with therapeutic potential. The particular antibody described here, as well as the technique developed to make additional functional antibodies to Eag1, makes it possible to evaluate the potential of the channel as a target for cancer therapy.

PMID: 17671204 [PubMed - indexed for MEDLINE]

Related Links

Role of voltage-gated potassium channels in cancer. [J Membr Biol. 2005]

Potassium channels as tumour markers. [FEBS Lett. 2006]

Overexpression of Eag1 potassium channels in clinical tumours. [Cancer. 2006]

Ether a go-go potassium channel expression in soft tissue sarcoma patients. [Mol Cancer. 2006]

Aberrant expression of ether a go-go potassium channel in colorectal cancer patients and cell lines. [Gastroenterol. 2007]

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1: Cancer Invest. 2007 Sep 11;;1-5 [Epub ahead of print]

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Antitumor Necrosis Factor (TNF-a) Antibodies in the Treatment of Renal Cell Cancer.

Maisey N.

Department of Academic Oncology, Guys Hospital, London, United Kingdom.

The kinase inhibitors sorafenib and sunitinib have demonstrated significant activity in renal cell carcinoma (RCC), and are now approved by the FDA for use in advanced disease. There still remains a need for novel therapies. Our group were the first to demonstrate activity of thalidomide in RCC, believed to be in part related to the modulation of tumor necrosis factor (TNF-a), a cytokine secreted by RCC with a number of tumor promoting properties. We subsequently conducted a phase II trial of the TNF-a monoclonal antibody infliximab in patients with previously treated advanced RCC. The drug was well tolerated. The response rate was 16% and stability was achieved in a further 16% of patients. Anti-TNF-a therapy may represent an important approach in the treatment of this disease.

PMID: 17852116 [PubMed - as supplied by publisher]

Related Links

Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. [Cancer Invest. 2007]

Clinical experience with CD64-directed immunotherapy. An overview. [Cancer Immunother. 1997]

Cytokine profiles during infliximab monotherapy in psoriasis. [J Invest Dermatol. 2005]

Transcending conventional therapies: the role of biologic and other novel therapies. [Inflamm Bowel Dis. 2001]

Sunitinib in patients with metastatic renal cell carcinoma. [JAMA. 2006]

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